Aprepitant, antiemetics, chemotherapy, substance P

ABSTRACT
Aprepitant (Emend, Merck Inc., Whitehouse Station, NJ), a neurokin-1 (NK1) receptor antagonist, is a first-in-class agent approved for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV). It competitively binds to NK1 receptors, blocks the binding of substance P, the natural ligand, and prevents signal transduction. Early clinical trials showed that aprepitant combined with standard therapy (corticosteroids and serotonin receptor antagonists) provided improved antiemetic protection in patients receiving highly emetogenic chemotherapy. The results of three randomized, double blind, placebo-controlled trials that compared aprepitant plus standard therapy with standard therapy plus placebo showed significant improvements in complete response rates (defined as no emesis and no use of rescue medication) with the addition of aprepitant (58.8% to 71% vs. 43.3% to 52.3%; P < .05 for all). Benefits were found in the acute phases, delayed phases, and in the overall study periods. Multiple secondary endpoints also favored the addition of aprepitant, particularly in the delayed phases and overall study periods. In extended trials in which treatment was continued for up to 6 cycles of highly emetogenic chemotherapy, the antiemetic effect was maintained and remained statistically greater for the aprepitant plus standard therapy group compared with standard therapy and placebo. The addition of aprepitant was well tolerated, and common adverse events were similar to those seen with standard therapy plus placebo. A clinically significant drug interaction with CYP3A4-metabolized cytotoxic agents was reported in one trial, but not confirmed in the others. The additional protection confirmed by aprepitant translated into a decreased impact of CINV on patients’ daily lives as measured by the Functional Living Index-Emesis questionnaire. Aprepitant adds additional antiemetic protection to standard therapy and should be considered in all patients receiving highly emetogenic chemotherapy. (JNCCN 2004;2:491–497)

In the past 15 years, significant advances have been made in the prevention of chemotherapy-induced nausea and vomiting (CINV). Despite these advances, the ultimate goal of antiemetic therapy—to completely prevent nausea and vomiting in all settings—remains elusive. Considerable numbers of patients continue to experience CINV, and recent evidence indicates health care professionals substantially underestimate the incidence of CINV and overestimate the degree of control. The antiemetics most effective in preventing CINV, serotonin (type 3 5-hydroxytryptamine) receptor antagonists (5-HT3 RA), corticosteroids, and dopamine receptor antagonists (metoclopramide), are used alone and in combination to prevent acute (occurring in the first 24 hours after chemotherapy administration) and delayed (occurring days 2 to 5 after chemotherapy administration) CINV. Multiple organizations have published evidence-based practice guidelines to facilitate the incorporation of these agents into clinical practice. Although these guidelines largely incorporate high level I recommendations to minimize CINV, adherence to these guidelines is not uniform. Despite an improved understanding of how to effectively use these agents, many patients still suffer distressing side effects. Not only are these symptoms physically and psychologically uncomfortable, they are associated with treatment delays, discontinuations, and greater financial costs. Better control of CINV can be achieved by both enhancing adherence to guidelines and by exploring drugs with new mechanisms of action. Improved understanding of the pathophysiologic mechanisms of CINV has resulted in the development of a new class of antiemetics, the neurokin-1 receptor antagonists (NK1...
RA). Aprepitant (Emend, L-754,030, MK-0869; Merck and Co Inc, Whitehouse Station, NJ) is the first drug in this class to receive Food and Drug Administration (FDA) approval and with an indication, in conjunction with other antiemetics, for preventing both acute and delayed CINV. The purpose of this article is to review the clinical experience with aprepitant in the prevention of CINV for patients receiving highly emetogenic chemotherapy.

Pathophysiology of CINV

Although comprehension of the pathophysiologic mechanisms of CINV has improved, overall knowledge is limited. Cytotoxic agents induce nausea and vomiting through multiple mechanisms, and these differ by agent. Agents may induce symptoms through peripheral, central, or a combination of peripheral and central pathways. The mechanisms involved in acute-phase CINV are believed to be different from those involved in delayed-phase CINV. Different mechanisms result in activation of the chemoreceptor trigger zone (CTZ) located in the area postrema of the brainstem. Once it is activated, neurotransmitters are released from the CTZ and stimulate the vomiting center. Dopamine, serotonin (5-HT), and substance P (SP) are neurotransmitters that have been extensively studied in connection with CINV. 5-HT is an important neurotransmitter in a well-described peripheral pathway. Highly emetogenic cytotoxic agents induce the release of 5-HT from enterochromaffin cells located in the gastrointestinal tract. The released 5-HT acts on adjacent abdominal afferent vagal nerves, induces depolarization and stimulation of the vomiting center in the brainstem.

The role of SP is a more recently described finding. A peptide of the neurokinin family, SP is found in vagal afferent nerves within the gastrointestinal tract and in regions of the central nervous system (CNS) involved in control of the vomiting reflex (the nucleus tractus solitarius and area postrema). The biologic effects of SP are mediated through a tachykinin receptor, NK1, a G-protein receptor coupled to the inositol phosphate signal-transduction pathway. A study finding that local administration of SP-induced vomiting in ferrets and that NK1 RA can inhibit this action supported the role of SP in the regulation of emesis. The basic function of the NK1 receptor is still not well-defined; NK1 receptor knock-out mice exhibit minimal, if any, abnormalities, and are developmentally normal and fertile. Different classes of antiemetics are effective against different mechanisms of CINV and, when used in combination, are more effective in preventing CINV caused by highly emetogenic chemotherapy than when used alone. 5-HT3 RA (dolasetron, granisetron, ondansetron, and tropisetron) now play an integral role in the prevention of acute CINV. These agents block 5-HT receptors on the abdominal afferent vagal nerves, preventing depolarization and further stimulation of the vomiting center within the brainstem. Metoclopramide, an agent effective in both acute and delayed CINV, antagonizes centrally-located dopamine receptors and at high doses inhibits 5-HT3 receptors. Corticosteroids, through unclear mechanisms of action, possibly anti-inflammatory effects, are also effective in both acute and delayed CINV. Despite combinations of these agents, a substantial portion of patients (30% to 50%) receiving highly emetogenic chemotherapy still experience nausea and vomiting, particularly during the delayed-phase. In addition to the inherent emetogenicity of a particular chemotherapeutic agent, other modifying risk factors for the development of CINV are recognized. These include major factors such as young age, female gender, and low alcohol consumption. Minor factors are a history of motion sickness or emesis with pregnancy.

Preclinical Studies and Pharmacology

The induction of emesis in ferrets through cisplatin administration is a model for CINV that was validated in the development of 5-HT3 RA and similarly used in the investigation of NK1 RA. Intravenous aprepitant prodrug and oral aprepitant significantly inhibit acute retching and vomiting in ferrets exposed to cisplatin. In an evaluation of the protective effects in acute and delayed-phases of CINV, aprepitant administered before cisplatin completely prevented acute retching and vomiting. When administered after cisplatin-induced emesis was already established, aprepitant prevented further retching and vomiting. With the efficacy of aprepitant established in the ferret model, pharmacokinetic studies and clinical trials were pursued.

Aprepitant is extensively metabolized in the liver and is both a substrate and a moderate inhibitor of the cytochrome (CYP) P450 3A4 system. In addition, it
induces CYP2C9, but has no effect on CYP2D6. A potential for drug interactions exists with 3A4 substrates, in particular, chemotherapy agents, dexa-
methasone and methylprednisolone (See subsequent sections). Warfarin (Coumadin, Bristol-Myers Squibb Company, Plainsboro, NJ) levels may be slightly re-
duced because of the CYP2C9 effect, and international normalized ratio (INR) monitoring is recommended for patients on warfarin. Aprepitant has no effect on the concomitantly administered 5-HT3 RA, granisetron, and ondansetron (CYP2D6 substrates).

Clinical Studies

Early phase clinical trials of aprepitant or its intra-
venous prodrug L-758,298 established the NK1 RA's tolerability and safety, and suggested that combination regimens of aprepitant, corticosteroids, and 5-HT3 RA have greater efficacy than single- or dual-agent regi-
mens. In all studies, aprepitant was well tolerated. Common adverse events reported in 10% or more of treated patients in at least one treatment arm in these trials were abdominal pain, anorexia, asthenia, con-
stipation, dehydration, diarrhea, dizziness, headache, and hiccups. In the three trials that included a treatment arm that did not receive a 5-HT3 RA (on-
dansetron or granisetron), diarrhea occurred numerically more often compared with arms treated with a 5-HT3 RA. No serious clinical adverse events believed to be attributable to the study drug occurred, and within each study, there were no significant dif-
ferences in laboratory measures of safety.

As clinical trials with aprepitant moved from early stage clinical trials to phase III trials, corticosteroids and a 5-HT3 RA prior to, and corticosteroids with or without 5HT3 RA or metoclopramide for 3 to 4 days after highly emetogenic chemotherapy became standard preventative therapy. The results of three large randomized trials comparing the addition of aprepitant to standard therapy to placebo plus standard therapy have been completed. In all three trials standard therapy included corticosteroid and 5-HT3 RA on day 1 and corticosteroids on days 2 to 4 or 5.

Chawla et al. reported the results of a large dose-
finding study. This was designed as a three-arm trial, and two dose schedules of aprepitant containing combi-
nation therapy were compared with standard therapy. All patients were treated with 32 mg intravenous ondansetron and 20 mg intravenous dexamethasone before cisplatin and 8 mg dexamethasone on days 2 to 5. The three arms included a 375/250-mg group treated with oral aprepitant 375 mg before cisplatin and 250 mg on days 2 to 5; a 125/80-mg group treated with oral aprepitant 125 mg before cisplatin and 80 mg on days 2 to 5; and a standard therapy arm treated with placebo before cisplatin and on days 2 to 5.

Although the study was ongoing, the 375/250-mg group was discontinued and replaced with a 40/25-mg group (40 mg aprepitant before cisplatin and 25 mg on days 2 to 5). This was done when new pharmacoki-
netic data from healthy volunteers revealed that the 375/250-mg doses resulted in plasma aprepitant levels that were higher than expected and higher than neces-
sary to block more than 90% of CNS NK1 receptor sites. The primary efficacy analysis focused on 381 pa-

tients randomized according to the final trial design and the primary study endpoint was complete response (defined as no emesis and no use of rescue medication) during the overall study period (days 1 to 5). Compared with standard therapy, complete responses were
significantly greater in each aprepitant group during the overall study period and during the delayed phase (Table 1). For the secondary endpoints of no emesis, no nausea, total control, and complete protection, both aprepitant-containing groups were significantly more effective than standard therapy during the overall study period. When the data were analyzed by phase (acute and delayed), the 125/80-mg group was statistically more effective for the endpoints of complete response, complete protection, and no emesis during the acute phase. During the delayed phase, the 125/80-mg group was statistically superior to standard therapy by all study endpoints. Compared with standard therapy, the 40/25-mg group was not statistically superior for any endpoint during the acute phase, but showed significantly improved control during the delayed phase, with numerical superiority by all study endpoints and significant benefit for complete response, no emesis, no rescue, no vomiting, complete protection, and total control. The overall incidence of adverse events was similar across all treatments groups. However, a higher incidence of infection was seen in the 125/80-mg group than in the standard therapy group (13% vs. 4%). Researchers hypothesized that this was caused by a pharmacokinetic interaction of aprepitant that resulted in greater exposure to dexamethasone. No drug interactions were reported. Overall, the trial showed that (1) the addition of aprepitant to standard therapy improved control of CINV and (2) the 125/80-mg doses provided greater protection than the 40/25-mg dose. Based on efficacy and tolerability, the aprepitant 125/80-mg dose was chosen as the appropriate regimen for further studies.

Two large, randomized, phase III, double-blind, placebo-controlled studies (052 and 054 studies) were initiated with similar entry criteria and dosing regimens. They both evaluated the addition of aprepitant to standard therapy during administration of an initial cycle of a cisplatin (dose, 70 mg/m² or greater)-containing chemotherapy regimen. The antiemetic dosing regimen was modified to account for the CYP3A4 interaction between aprepitant and dexamethasone and approximate equivalent dexamethasone exposure in both arms. Patients in the control group received intravenous ondansetron 32 mg and oral dexamethasone 20 mg on day 1, followed by oral dexamethasone 8 mg twice daily on days 2 to 4. Patients in the aprepitant group received oral aprepitant 125 mg plus intravenous ondansetron 32 mg and oral dexamethasone 12 mg on day 1, oral aprepitant 80 mg and oral dexamethasone 8 mg once daily on days 2 and 3, and oral dexamethasone 8 mg on day 4.

The Aprepitant Protocol 054 Study was largely conducted in Latin America. In this study, 569 patients were randomized to receive one of the two treatment groups specified previously. As in the Chawla et al. study, the complete response rate during the overall study period was the primary endpoint (Table 1). The study showed that 62.7% of the aprepitant-treated patients, as compared with 43.4% of the control group, showed a complete response (P < .001). When analyzed by time intervals, complete responses were greater in the both the acute (82.8% vs. 68.4%; P < .001) and delayed-phases (67.7% vs. 46.8%; P < .001).

For the secondary endpoints, the aprepitant arm had a significantly greater number of patients with no nausea in both the delayed phase and the overall study period. Additionally, a significantly greater number of patients with complete protection (no emesis, no rescue medication, and no significant nausea) at all time points were noted in the aprepitant arm. No differences were seen in the toxicity profiles of each arm in terms of clinical adverse events, drug-related clinical adverse events, serious clinical adverse events, laboratory adverse events, drug-related laboratory adverse events, and discontinuations. The steroid doses used in this study were lower than those in the Chawla et al. study, and no increase in infectious complications was noted. A possible drug interaction was reported in patients who received concomitant treatment with a CYP3A4 metabolism-dependent chemotherapeutic agent (etoposide, vinorelbine, and taxanes); in this subgroup, the incidence of serious adverse events was greater in the aprepitant arm compared with standard therapy (15.8% vs. 8.5%). In contrast, the incidence was lower in the aprepitant treated arm for patients who did not receive concurrent CYP3A4 metabolized chemotherapy (4.2% vs. 11.6%).

The third large study to evaluate the addition of aprepitant to standard therapy was reported by the Aprepitant 052 Study Group. In this multinational phase III study, 530 patients were randomized to the same treatment groups as in the 054 Study. Again, findings showed statistically significant benefits favoring the aprepitant arm in terms of complete responses for the overall study period (72.7% vs 52.3%; P < .001), the acute (89.2% vs. 78.1%; P < .001), and
the delayed-phases (75.4% vs 55.8%; P < .001; Table 1). Secondary endpoint data showed significantly greater responses in the aprepitant arm at all time points for the endpoints of no emesis, no rescue, and complete protection. The toxicity profiles of each arm were similar, and the common clinical adverse events reported in at least 10% in one treatment arm were asthenia-fatigue, constipation, hiccups, and nausea occurring after day 5. In contrast to the 054 Study, no increased incidence of serious adverse events in patients treated with concomitant CYP3A4 metabolized chemotherapeutic agents was reported in the 052 Study. In summary, all three large, randomized, placebo-controlled, trials demonstrated significant improvement in control of CINV with the addition of aprepitant to standard therapy.

A combined analysis of the 052 and 054 studies showed that, in addition to the superiority of the aprepitant regimen, with the addition of aprepitant to standard therapy, no gender difference was seen in complete response rates after highly emetogenic chemotherapy. Results showed that 86% of women versus 87% of men achieved a complete response with aprepitant; however, only 66% of women and 80% of men achieved a complete response in the control group.

Studies 052, 054, and the Chawla et al. study all evaluated the efficacy of aprepitant as part of combination antiemetic therapy during the initial cycle of cisplatin containing chemotherapy in cisplatin-naïve patients. In an extension phase of the Chawla et al. study, de Wit et al. reported on the efficacy of aprepitant-containing combination therapy over multiple cycles (up to 6) of cisplatin-containing chemotherapy. The 202 patients randomized by the initial trial design were reported on in the extension phase of the study. Comparing the 125/80-mg group and the standard arm, complete responses during cycle 1 were achieved in 64% and 49%, respectively (P < .05). During cycles 5 and 6, the complete response rate remained statistically greater for the 125/80-mg arm (59% vs. 34%; P < .05). Although the efficacy of the 125/80-mg group was maintained from cycle 1 to 6 (complete responses of 64% and 59%), the response rate of standard therapy decreased by 15% between cycles 1 and 6 (49% and 34%). No formal comparisons were made for the 375/250-mg group, but complete responses rates during cycles 1 and 6 were similar to those of the 125/80-mg group. The finding of similar efficacy of these two treatment groups is concordant with results from a positron-emission tomography imaging study that showed L-758,298 doses of 300-mg and 125 mg were equally effective in blocking 90% or more of CNS NK1 receptors.

No statistically significant differences in adverse events were reported between the treatment arms. However, numerically, more serious adverse events occurred over cycles 2 to 6 in the 125/80-mg group. These were not reported as attributable to the study drug. The increase is accounted for by a greater number of febrile neutropenic and infection-related adverse events in the aprepitant group. Again, this is thought to be caused by a pharmacokinetic interaction of aprepitant that results in increased corticosteroid levels. The steroid dose used in the delayed-phase was lower in studies 052 and 054 than in the de Wit et al. or Chawla et al. studies, and no increased rates of serious adverse events, febrile neutropenia, or infection-related adverse events were found.

De Wit et al. published a second, similar extension study that combined patients enrolled in Studies 052 and 054. The study’s primary endpoint, a combined exploratory endpoint of no emesis and no significant nausea, was evaluated for up to 6 cycles of cisplatin-based chemotherapy. Using a cumulative probabilities approach, the estimated probability rates of no emesis and no significant nausea were significantly greater across all cycles for the aprepitant-treated patients compared with patients receiving standard therapy (61% vs. 46%; P < .001; 59% vs. 40%; P < .001, for cycles 1 and 6, respectively). The toxicity profiles of the treatment groups were comparable and no cumulative toxicities attributable to aprepitant were identified. This second study confirmed the improved antiemetic control with continued aprepitant use during multiple cycles of highly emetogenic chemotherapy.

The Functional Living Index-Emesis (FLIE) questionnaire was administered in the 052, 054, and Chawla et al. studies to evaluate the impact of CINV on patients’ daily lives. This is a validated nausea and vomiting-specific patient-reported outcome measure. The FLIE results were significantly better for aprepitant groups compared with standard therapy in all studies (Table 2). In the 054 study, 74.7% and 63.5% of aprepitant versus standard therapy patients had scores consistent with “minimal or no impact of CINV on daily life.”
The 052 Study results for the same outcome measure were 74.0% and 64.3% for the aprepitant and standard therapy arms, respectively. The FLIE results from the Chawla et al. study were reported separately, and for the primary endpoint of “no impact on daily life” the results again favored the aprepitant (125/80-mg) group. FLIE data from these studies suggest an absolute increase of at least 10% in the number of patients who have “minimal or no impact on daily life” associated with the addition of aprepitant to standard therapy for cancer patients treated with highly emetogenic chemotherapy.

Conclusions

The addition of aprepitant to corticosteroids and 5-HT3 RA as prevention for CINV has been shown repeatedly to provide significantly improved control for cancer patients treated with cisplatin-based therapy. With triple-agent combination therapy, more patients are able to complete treatment with minimal impact on daily life. The therapy is generally well tolerated and the common side effects are similar to those of standard therapy; the common adverse events encountered include anorexia, asthenia-fatigue, constipation, diarrhea, hiccups, and nausea after day 5. The question of a possible drug interaction with CYP3A4 metabolized chemotherapeutic agents remains and continues to be evaluated. The use of aprepitant should be considered in all cancer patients undergoing treatment with highly emetogenic chemotherapy. Studies to evaluate whether these benefits are also realized with moderately emetogenic therapy are now complete and currently being analyzed.

References

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